CRP and Calprotectin

Karen Kroeker

Faculty Disclosure

• Faculty: Karen Kroeker

• Relationships with commercial interests:
  − Grants/Research Support: FLIBD
  − Speakers Bureau/Honoraria: Abbvie, Warner Chilcott, Shire
  − Consulting Fees: Baxter, Janssen Canada, Ferring, Shire
  − Other: None
Objectives

1. Understand the role of biomarkers in the diagnosis and management of patients with IBD
2. Discuss CRP – what does it mean?
3. Describe calprotectin in assessing active GI disease

TRIVIA: What do CRP & Sea stars have in common?

Biomarkers & IBD

• Currently, there is no “gold standard” test for IBD
• A good biomarker would help us be more objective in our assessment (cf assessment of symptoms which are subjective) and less invasive than endoscopy
• A good biomarker is:
  1. Easy and rapid to perform (minimally invasive)
  2. Cheap
  3. Reproducible (b/w pts and labs)
• CRP & Fecal Calprotectin are 2 biomarkers used in IBD

Gut 2006;55:426–431

C-REACTIVE PROTEIN
What is CRP?

- Acute phase protein, sensitive marker of inflammation
  - Named for its capacity to precipitate the somatic C-polysaccharide of Streptococcus pneumoniae
- Produced by hepatocytes, primarily under the control of IL-6
- Half-life ~19 hours
  - Rises quickly within 6 hours, peaks at 48 hours
- CRP gene (chr. 1), has many polymorphisms, may account for baseline variation

Understanding CRP

- Non-specific marker of inflammation
  - Few drugs reduce CRP unless they also affect the underlying pathology causing the increased CRP
- The hs-CRP (used in CV disease) is not a different molecule; it just means the assay has a lower limit of detection
- BMI is associated with baseline CRP
  - Weight loss lowers CRP
  - Raised baseline CRP is associated with insulin resistance or metabolic syndrome
  - Adipocytes are the source of most of baseline IL-6

Acute Phase Reactants

<table>
<thead>
<tr>
<th>Protein class</th>
<th>Increased</th>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protease inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute phase reactants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complement proteins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Properdin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transport proteins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C reactive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transferrin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CRP Diseases

<table>
<thead>
<tr>
<th>Table 1</th>
<th>CRP responses in disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major CRP acute-phase response</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Allergic complications of infection</td>
<td></td>
</tr>
<tr>
<td>Inflammatory disease</td>
<td></td>
</tr>
<tr>
<td>Features</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
</tr>
<tr>
<td>Moderate or absent CRP acute-phase response</td>
<td></td>
</tr>
</tbody>
</table>


CRP & IBD

- Elevated CRP is associated with symptoms and endoscopic active disease for both CD & UC
- Cut-offs have been suggested (mild: 10-50; moderate: 50-80, severe: >80 mg/l), but it is more important to compare with pt’s previous levels
- Elevated CRP can predict risk of surgery (Oxford Rule)
- Elevated CRP predicts response to anti-TNF therapy


CALPROTECTIN
What is Calprotectin?

- 1st described in 1980
- Calcium and zinc binding protein found in the cytosol of neutrophils (and macrophages)
- Found in plasma, urine, CSF, feces, saliva, etc.
- Is a DAMP protein (damage associated molecular pattern); released by the innate immune system by damaged or activated cells
- Fecal calprotectin is raised in any GI inflammatory process, including IBD

Uses for Fecal Calprotectin

- Distinguish IBD vs. IBS
- Distinguish active and quiescent disease in IBD
- Assessing response to treatment of IBD
- Predict relapse in patients with IBD
Fecal Calprotectin Can Distinguish IBD from Controls & IBS

Journal of Crohn's and Colitis (2012) 6, 207–214

Calprotectin – Algorithm for IBD

A

B

US Study – Effectiveness & Cost-Effectiveness
- FC saved $400/pt but delayed diagnosis in 7%
- Cost-effectiveness depended on the pre-test probabilities
  - If pre-test prob < 75% → cost-effective
  - If pre-test prob > 85% → not cost-effective
- Using a lower FC cut-off (50 v. 100 ng/mL) → improved accuracy in diagnosis 95% v. 87% (not including delayed Dx, but cost an additional $55/pt)

Clin Gastro Hep 2014 epub
Fecal Calprotectin in UC

• Correlation of non-invasive markers with endoscopic activity in UC
  - FC (r=0.821) was the best, Lichtiger Index (r=0.682), CRP (r=0.556), platelets (r=0.488), WBC(r=0.401), and hemoglobin (r=0.388)
  - Only fecal calprotectin was able to discriminate between grades of endoscopic severity
    - grade 0, 0–10 (mg/g) (normal)
    - grade 1, 15–29 (mg/g) (granular, loss of vasc pattern)
    - grade 2, 30–74 (mg/g) (friable, but not spontaneous bleeding)
    - grade 3, 75–123 (mg/g) (microulcerations, spont. bleeding)
    - grade 4, 124–611 (mg/g) (gross ulcerations, denuded mucosa)

Inflamm Bowel Dis 2013;19:332–341

FC & Endoscopic Activity

Inflamm Bowel Dis 2013;19:332–341

Fecal Calprotectin in CD

• Fecal calprotectin can predict disease severity in Crohn's disease, but with lower sensitivity and specificity than UC
• It is better in colonic than ileal disease
• Fecal calprotectin was just as good as CRP + fecal calprotectin

Inflamm Bowel Dis 2012;18:2218–2224
**Summary**

- Biomarkers, like CRP and fecal calprotectin are non-invasive markers that are helpful in the management of IBD
  - CRP
    - Advantages: Readily available
    - Disadvantages: Not everyone makes CRP, not-specific for the gut

**Summary (2)**

- Fecal Calprotectin
  - Advantages:
    - More specific for intestinal inflammation
    - Quick
    - Less invasive
  - Disadvantages:
    - Not readily available (yet)
    - Requires a stool sample (patients don't often like this)

**QUESTIONS?**